



AFRL-RH-WP-TN-2010-0001

THE EFFECTS OF EXERCISE ON BRAIN INFLAMMATION

2d Lt Megan C. Durbin

Air Force Research Laboratory, 711th Human Performance Wing

**JUNE 2010
Interim Report**

Approved for public release, distribution is unlimited.

See additional restrictions described on inside pages

**AIR FORCE RESEARCH LABORATORY
711TH HUMAN PERFORMANCE WING,
HUMAN EFFECTIVENESS DIRECTORATE,
WRIGHT-PATTERSON AIR FORCE BASE, OH 45433
AIR FORCE MATERIEL COMMAND
UNITED STATES AIR FORCE**

NOTICE AND SIGNATURE PAGE

Using Government drawings, specifications, or other data included in this document for any purpose other than Government procurement does not in any way obligate the U.S. Government. The fact that the Government formulated or supplied the drawings, specifications, or other data does not license the holder or any other person or corporation; or convey any rights or permission to manufacture, use, or sell any patented invention that may relate to them.

This report was cleared for public release by the 88th Air Base Wing Public Affairs Office and is available to the general public, including foreign nationals. Copies may be obtained from the Defense Technical Information Center (DTIC) (<http://www.dtic.mil>).

AFRL-RH-WP-TN-2010-0001 HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION IN ACCORDANCE WITH ASSIGNED DISTRIBUTION STATEMENT.

//SIGNED//

MEGAN C. DURBIN, 2d LT
Research Chemist, Vulnerability Analysis Branch
711 HPW/RHPA

//SIGNED//

Mark M. Hoffman
Biosciences and Performance Division
Human Effectiveness Directorate
711th Human Performance Wing
Air Force Research Laboratory

This report is published in the interest of scientific and technical information exchange, and its publication does not constitute the Government's approval or disapproval of its ideas or findings.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE (DD-MM-YY) 02-06-10			2. REPORT TYPE Interim	3. DATES COVERED (From - To) July 2009 – December 2009	
4. TITLE AND SUBTITLE THE EFFECTS OF EXERCISE ON BRAIN INFLAMMATION			5a. CONTRACT NUMBER In-House		
			5b. GRANT NUMBER		
			5c. PROGRAM ELEMENT NUMBER 62202F		
6. AUTHOR(S) Megan Durbin			5d. PROJECT NUMBER 7184		
			5e. TASK NUMBER A0		
			5f. WORK UNIT NUMBER 7184A001		
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) 711 th HPW/RHPA 2800 Q Street, Bldg 824 Wright Patterson AFB, OH 45433			8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES) Air Force Materiel Command Air Force Research Laboratory 711 th Human Performance Wing Human Effectiveness Directorate Biosciences and Performance Division Vulnerability Analysis Branch Wright-Patterson Air Force Base, OH 45433			10. SPONSORING/MONITORING AGENCY ACRONYM(S) 711 HPW/RHPA		
			11. SPONSORING/MONITORING AGENCY REPORT NUMBER(S) AFRL-RH-WP-TN-2010-0001		
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release; distribution is unlimited.					
13. SUPPLEMENTARY NOTES Technical Report written by RHPA military personnel to serve as review paper. 88ABW/PA cleared 15 Jul 10, 88ABW-2010-3794					
14. ABSTRACT Exercise is evolving as a therapeutic measure for both general health and brain health. Exercise reduces the risk of many systemic diseases and has been shown to improve cognition and memory. The mechanisms through which exercise achieves these positive neurologic results is unclear, but may involve the inflammatory cascade in the brain. This paper reviews the effects of exercise on the inflammatory cascade within the brain.					
15. SUBJECT TERMS Exercise, brain inflammation, brain health					
16. SECURITY CLASSIFICATION OF: a. REPORT Unclassified		b. ABSTRACT Unclassified	c. THIS PAGE Unclassified	17. LIMITATION OF ABSTRACT: SAR	18. NUMBER OF PAGES 23
				19a. NAME OF RESPONSIBLE PERSON (Monitor) Megan Durbin	
				19b. TELEPHONE NUMBER (Include Area Code) N/A	

THIS PAGE IS INTENTIONALLY LEFT BLANK

Table of Contents

<u>Section</u>	<u>Page</u>
1. Introduction.....	1
2. Discussion.....	2
3. Conclusion	12
4. References	13

THIS PAGE IS INTENTIONALLY LEFT BLANK

INTRODUCTION

Exercise is evolving as an effective therapeutic measure for both general health and brain health. It has been established that exercise and a healthy lifestyle can reduce the risk of diseases such as diabetes mellitus and atherosclerosis (Petersen and Pedersen 2005). In the past decade, overwhelming research has shown that exercise can improve learning and memory, delay age-related cognitive decline and reduce risk of neurodegeneration (Cotman, Berchtold et al. 2007). Animal research has demonstrated that physical activity increases neuronal survival, promotes brain angiogenesis, stimulates neurogenesis and reduces injury following brain insult (Cotman, Berchtold et al. 2007; Ding, Mrizek et al. 2006; van Praag 2008; Carro, Trejo et al. 2001; Nickerson, Elphick et al. 2005). Human research has shown that exercise can reduce the risk of cognitive impairment, depression, Alzheimer's disease and other forms of dementia (Cotman, Berchtold et al. 2007). The methods by which exercise achieves these goals are complex and not yet completely understood, but research shows that exercise-induced effects on the inflammatory cascade may contribute.

Inflammation is a key defense mechanism in response to stress, injury or infection and involves a complex interplay between mediators such as cytokines, growth factors and reactive oxygen species. While inflammation is intended to promote recovery from the initial insult, the process can damage bystander neurons and thus worsen the original injury if not appropriately regulated. Thus, inflammation can be both neuroprotective and neurotoxic. Inflammation in the brain is unique from that in the periphery because of the protection afforded by the blood-brain barrier (BBB), which only allows certain molecules and cells to enter and exit (Morganti-Kossmann, Rancan et al. 2002; Whitney, Eidem et al. 2009). After a brain injury, activated microglia, astrocytes, macrophages and lymphocytes release pro-inflammatory cytokines such as interleukin-1 β and tumor necrosis factor alpha that induce the subsequent inflammatory cascade. These pro-inflammatory cytokines are responsible for weakening the BBB so that effector cells from the periphery can enter the CNS. Anti-inflammatory interleukins such as interleukin-10 are expressed as well to regulate the process. The inflammation cascade consists of additional cytokines, growth factors and reactive oxygen species that serve to clear dead or damaged cells and return the area to a normal state (Whitney, Eidem et al. 2009). The inflammatory process is paramount in determining the degree of tissue destruction and functional impairment after an insult. This review will focus on the effects of exercise on several mediators involved in the inflammatory cascade.

DISCUSSION

IL-1 β

Interleukin-1 β (IL-1 β) is a pro-inflammatory cytokine and a principle mediator of the inflammatory response. Secreted mainly by activated macrophages, the IL-1 family consists of two ligands, IL- α and IL- β , but the IL-1 β ligand is more potent in brain inflammation and will be reviewed here (Tsakiri, Kimber et al. 2008). IL-1 β increases with ischemia, traumatic brain injury and neurodegenerative processes such as Alzheimer's disease (Wang and Schuaib 2002; Nichol, Poon et al. 2008). The negative effects of IL-1 β are diverse and include fever, anorexia, increased adrenocorticotropic hormone (ACTH) and cortisol production, system hypotension, and stimulation of IL-6 and IL-8 (Sharma, Mishra et al. 2007; Smith, Anwar et al. 2000). IL-1 β also induces leukocyte adhesion and subsequent tissue infiltration via up-regulation of adhesion molecules ICAM-1 and VCAM-1 (Krakauer 1995). While IL-1 β can be detrimental during inflammation by causing microvascular injury and contributing to cerebral edema, it may aid recovery by promoting angiogenesis and activating astrocytes to re-establish homeostasis (Wang, Olschowka et al. 1997).

The effects of exercise on IL-1 β levels are varied in the literature. Twelve weeks of aerobic training in humans with coronary artery disease resulted in decreased plasma levels of IL-1 β (White and Castellano 2008). High-intensity eccentric muscle exercises in healthy male subjects decreased IL-1 β plasma concentrations lasting up to 144h (Smith, Anwar et al. 2000). Nichol et al studied the effects of exercise on Tg2576 mice, which are bred to manifest Alzheimer's disease (AD) (Nichol, Poon et al. 2008). Sedentary mice controls were found to have elevated levels of hippocampal IL-1 β , which was expected since IL-1 β is elevated in AD. Tg2576 mice with access to running wheels for 3 weeks, however, had decreased levels of hippocampal IL-1 β not significantly different from wild-type controls. Since elevated levels of IL-1 β in the hippocampus correlate with decreased performance in spatial navigation and declarative memory (Oitzl, van Oers et al. 1993; Nichol, Poon et al. 2008), these findings may suggest a beneficial effect of exercise on the cognitive functions of AD patients.

Several studies have shown no effect of exercise on IL-1 β plasma concentrations. Natelson et al studied 7 men after a maximal treadmill stress test and found no difference between pre- and post-exercise plasma levels of IL-1 β (Natelson, Zhou et al. 1996). Mice exercised for 60 minutes or 3 hours on a treadmill before sacrifice showed no change in plasma or brain concentrations of IL-1 β (Colbert, Davis et al. 2001). Mice progressively trained for 7 weeks demonstrated stable plasma IL-1 β but decreased hippocampal levels (Chennaoui, Drogou et al. 2008). It may be that prolonged exercise is necessary to decrease tissue levels of IL-1 β .

While the above studies revealed decreased or stable IL-1 β levels, other studies report increased levels after exercise. In a study of humans cycling for 3 periods of 6 minutes each (55%, 70% and 85% VO₂ max, respectively), plasma IL-1 β was found to be increased as early as 6 minutes after exercising regardless of fitness level and returned to baseline after 2 hours of recovery (Moyna, Acker et al. 1996). A study of horses subjected to treadmill running until fatigued had increased leukocyte expression of IL-1 β mRNA that persisted for at least two hours (Donovan, Jackson et al. 2007).

The controversy in the literature may result from several factors including the model used, the duration and intensity of exercise, and the measurement techniques. The above studies were performed in a variety of test models, with inflammatory mechanisms that may respond differently to exercise. It may be that acute exercise of certain duration and intensity causes a mild endotoxemia that acutely increases IL-1 β (Donovan, Jackson et al. 2007) but chronic exercise causes the body to become sensitized to the stress of exercise and produce less. Exercised rats (voluntary running wheels for 6 weeks) sacrificed after an intraperitoneal injection of lipopolysaccharide had a greater and more rapid up-regulation of central IL-1 β after 30 minutes, less endotoxin and faster clearance of E coli versus the sedentary controls (Nickerson, Elphick et al. 2005). Additionally, circulating IL-1 β peaked in sedentary animals 6 h after the E coli challenge but was not elevated in exercised animals. The increase in central IL-1 β and the rapid clearance of toxin suggest that exercise-induced-sensitization has beneficial effects after injury (Nickerson, Elphick et al. 2005). A study by Mussi et al examined the effect of exercise on pulmonary ischemia-reperfusion injury in rats, and found that exercise preconditioning on a treadmill resulted in reduced serum IL-1 β and attenuated protein extravasation in lung tissue versus non-exercised controls (Mussi, Camargo et al. 2008) during reperfusion. Thus, exercise may produce a low level of chronic inflammation that leads to more efficient response to injury.

The ability to accurately measure protein concentrations in plasma depends on the amount of cytokine unbound and the protocol used to measure. Additionally, cytokines are rapidly cleared from the circulation, so timing differences after exercise may affect outcomes (Smith, McKune et al. 2007). These issues exist for all inflammatory mediators discussed in this review and must be considered when interpreting study results. IL-1 β is known to accumulate intra-cellularly before the release stimulus is received, so if exercise caused an intracellular accumulation of IL-1 β , plasma levels would be misleading (Smith, McKune et al. 2007).

TNF- α

Tumor necrosis factor alpha (TNF- α) is a pro-inflammatory cytokine that increases after injury and can lead to neuronal death (Goodman, Robertson et al. 1990). TNF- α is produced by activated astrocytes and microglia and is associated with a variety of downstream signaling cascades (Ang and Gomez-Pinilla 2007). Like IL-1 β , TNF- α up-regulates the expression of adhesion molecules such as ICAM-1, thereby promoting leukocyte adhesion to endothelial cells and increased capillary permeability (Barone, Arvin et al. 1997; Ozenci, Kouwenhoven et al. 2002). Rapid elevations of TNF- α after ischemic brain injury are associated with greater lesion volume and poor neurological and functional outcomes (Fassbender, Rossol et al. 1994; Barone, Arvin et al. 1997; Ding, Young et al. 2005).

Several studies have shown an increase in TNF- α with exercise. Adult rats exercised on a treadmill for 3 weeks had gradually rising, significant increases in frontoparietal cortex and dorsolateral neostriatum TNF- α mRNA and protein (Ding, Li et al. 2006; Ding, Young et al. 2005). After transient ischemia, exercised rats had reduced infarct volume and a significant reduction in brain edema suggesting improved cerebrovascular integrity (Ding, Li et al. 2006). TNF- α levels did not increase further after the ischemic event in exercised rats, whereas a spike was observed in non-exercised controls (Ding, Young et al. 2005). The TNF- α spike was associated with an increase in ICAM-1, whereas ICAM-1 levels in exercised animals remained significantly lower during reperfusion thereby decreasing leukocyte infiltration and reducing

infarct volume (Ding, Young et al. 2005). Furthermore, brain damage in exercised ischemic rats was limited to the ischemic core, whereas non-exercised ischemic rats had extensive infarcted areas (Ding, Young et al. 2005). Similar results were seen in exercised rats pretreated with gradually increasing TNF- α doses, suggesting that the gradual increase in TNF- α seen with exercise is neuroprotective after ischemic brain injury (Ding, Li et al. 2006). Guo et al also studied TNF- α levels after exercise and transient ischemia (Guo, Lin et al. 2008). Adult male rats subjected to treadmill running for 3 weeks before a transient ischemic event had increased TNF- α , increased collagen IV, and decreased matrix metalloproteinase-9 levels correlating with decreased infarct volume, brain edema, and Evans blue extravasation across the BBB. All of these effects were blocked by TNF- α inhibitors. Thus, the gradual increase of TNF- α with exercise seems to reduce brain injury after ischemia and reperfusion via multiple mechanisms.

Generally, single bouts of exercise have not been shown to change plasma or tissue TNF- α levels. Romeo et al studied 22 young males after a single bout of intense exercise and observed no change in plasma TNF- α (Romeo, Jimenez-Pavon et al. 2008). Colbert et al studied plasma and brain samples of mice after moderate and fatiguing exercise on treadmills and found no significant increase in TNF- α in either group (Colbert, Davis et al. 2001). Dalsgaard et al examined arterial-venous ratios of TNF- α across the brain after strenuous arm and leg exercises in humans, and found no difference in TNF- α levels (Dalsgaard, Ott et al. 2004).

These studies support the theory that TNF- α rises gradually with chronic exercise, and that the gradual rise is able to protect the brain from further injury such as ischemia. It is unclear what duration and intensity of exercise is required to induce the increase or how long the TNF- α remains elevated once exercise ceases. It is also unknown whether the body eventually adapts to one form of exercise and TNF- α levels decrease again. Stroke is the third leading cause of death in the USA and many survivors are left with physical and mental disabilities (Ding, Mrizek et al. 2006). The fact that exercising before ischemia can decrease infarct volume in rodents may have important and exciting implications for humans and their functional outcomes after stroke.

IL-6

Interleukin-6 (IL-6) is a pleiotropic cytokine with both pro- and anti-inflammatory properties (Nybo, Nielsen et al. 2002; Ozenci, Kouwenhoven et al. 2002). IL-6 is normally low in the CNS but increases during brain injury, hypoxia and certain diseases (Nybo, Nielsen et al. 2002; Van Wagoner and Benveniste 1999). The predominant CNS source of IL-6 is the activated astrocyte and the peripheral source is contracting skeletal muscle (Nybo, Nielsen et al. 2002; Van Wagoner and Benveniste 1999). Centrally, there is evidence of IL-6 promoting neuronal survival, protection and differentiation (Van Wagoner and Benveniste 1999). However, over-expression contributes to an increased production of central inflammatory cytokines and astrocyte proliferation, which leads to reactive gliosis found in white matter diseases (Van Wagoner and Benveniste 1999). Peripherally, IL-6 increases insulin-stimulated glucose disposal and fatty acid oxidation in humans (Nielsen and Pedersen 2007).

There is controversy in the literature regarding the effects of exercise on IL-6 concentrations both in brain tissue and plasma. Castaneda et al found a reduction in resting plasma IL6 in patients with kidney disease after 12 weeks of resistance training (Castaneda, Gordon et al. 2004). Goldhammer et al found that 12 weeks of aerobic training in coronary

artery disease patients reduced resting plasma IL6 (Goldhammer , Tanchilevitch et al. 2005). Colbert et al studied IL6 plasma and tissue concentrations in mice after either 60 minutes or 3 hours of running on a treadmill (Colbert, Davis et al. 2001). IL6 was increased in the plasma of mice run for 3 hours, but was undetectable in plasma and brain tissue of controls and mice run for only 60 minutes. Nybo studied human subjects exercised on a cycle ergometer (50% VO₂max) and saw no net release or uptake of IL6 in the brain at rest or after 15 minutes of exercise, but observed a small release after 60 minutes of exercise that returned to baseline during rest (Nybo, Nielsen et al. 2002). After 60 min of rest, a second bout of cycling resulted in a 5-fold increase in IL-6 release from the brain. There was an increase in arterial IL-6 during both the first and second bouts of exercise.

Another study looked at the arterial-venous ratio and the cerebrospinal fluid (CSF) levels of IL6 in humans subjected to arm and leg exercises until exhaustion (Dalsgaard, Ott et al. 2004). Blood samples drawn at rest, at exhaustion, and 30 minutes into recovery showed an increase in arterial concentration of IL-6 but no difference in the a-v ratio, suggesting no release or uptake by the brain. The IL-6 concentration in CSF did not change compared to resting controls. Thus, it appears that acute exercise of appropriate duration and intensity increases plasma IL-6 concentrations but chronic exercise leads to reduced levels.

Nybo's study suggests that increased duration of exercise is required to observe CNS release of IL6. Steensberg et al also looked at the effects of exercise on plasma and CSF IL6 in humans and found that 2 h of strenuous exercise on a cycle ergometer (60% VO₂ max) increased plasma IL6 18 fold but did not affect CSF concentrations (Steensberg, Dalsgaard et al. 2006). Banks et al studied the transport of IL6 across the BBB in mice and found that, while the BBB contains bidirectional IL6 transport molecules, only 0.2% of radio-labeled IL6 entered the CSF after IV injection (Banks, Kastin et al. 1994). However, neurons in the median eminence and circumventricular organs in the hypothalamus do not contain a BBB, so plasma concentrations of IL-6 may directly affect these brain areas (Steensberg, Dalsgaard et al. 2006). Additionally, plasma IL-6 levels above 40 pg/mL in humans stimulate the production of corticotropin releasing hormone, growth hormone, and prolactin (Robson-Ansley, de Milander et al. 2004), indicating that elevations in plasma IL-6 still affect central functions. Plasma levels of IL-6 above 40 pg/mL are seen in humans during infection or prolonged strenuous exercise such as marathon running (Febbraio and Pedersen 2002).

Overall, plasma IL6 concentrations appear to rise acutely with appropriate duration and intensity of exercise then return to baseline. Chronic exercise appears to result in decreased IL6 plasma concentrations. Because IL6 is believed to originate from contracting skeletal muscle, it is logical that levels would increase acutely with intense exercise. Peripherally, it is thought that low glycogen content in contracting skeletal muscle is the stimulus for IL6 production (Nybo, Moller et al. 2003) which in turn leads to hepatic glycogenolysis and glucose release. Glucose ingestion during exercise attenuates the release of IL6 from muscles, further supporting this theory (Secher, Seifert et al. 2008). Therefore, it may be that chronic exercise leads to skeletal muscle conditioning and changes in glucose homeostasis that decrease the need for IL6.

If the stimulus for muscle production of IL6 is hypoglycemia, it is tempting to think that may be the same stimulus for central production since the human brain consumes carbohydrates

out of proportion to oxygen during and following exercise (Dalsgaard, Ott et al. 2004). However, IL6 release from the brain was recently demonstrated to diminish during prolonged exercise with hypoglycemia compared to prolonged exercise with glucose supplementation, suggesting that factors other than glucose metabolism are involved in CNS release of IL6 (Nybo, Moller et al. 2003). Also, given the vastly reduced concentration of central versus peripheral IL6, it may be that central IL6 has a biological function other than glucose homeostasis (Nybo, Moller et al. 2003). Wallenius et al studied the effects of intracerebroventricular IL6 injection into the lateral ventricle of rats, and found that the injection led to increased basal oxygen consumption for 3 hours (Wallenius, Wallenius et al. 2002). Thus, it may be that central IL6 levels are involved in oxygen rather than glucose homeostasis. At this time the stimulus and role of exercise-induce central IL-6 remains speculative.

IL-10

Interleukin-10 (IL-10) is a primary anti-inflammatory cytokine that is up-regulated in over a dozen central and peripheral diseases and disorders (Vitkovic, Maeda et al. 2001). IL-10 promotes neuronal survival and limits inflammation by reducing the synthesis of pro-inflammatory cytokines, suppressing cytokine receptor expression, and inhibiting receptor activation (Strle, Zhou et al. 2001). Produced by a subset of T helper cells (Th2), mast cells and macrophages, IL-10 also inhibits adhesion of leukocytes to endothelium by counteracting the effect of IL-1 β on adhesion molecules (Krakauer 1995).

Catecholamines and glucocorticoids released during exercise stimulate the production of IL-10 in a response generally observed to be proportional to exercise intensity (White and Castellano 2008; Peake, Suzuki et al. 2005). Smith et al studied healthy males performing eccentric exercises and found an increase in IL-10 lasting at least 144 h after exercise completion (Smith, Anwar et al. 2000). In a separate study, male subjects had a 95% increase in serum IL-10 after downhill running (Smith, McKune et al. 2007). Peake et al examined the intensity of exercise required to produce an increase in IL-10, and found that high-intensity running on a treadmill resulted in increased levels but moderate-intensity and downhill running did not (Peake, Suzuki et al. 2005). Notably, the subjects in Smith's downhill run study were untrained subjects at a -13.5% grade for 60 min, whereas the subjects in Peake's study were trained athletes run at a -10% grade for 45 min. Nieman et al studied 12 athletes after 2h of intensive cycling and found IL-10 gene expression to be increased in blood leukocytes (Nieman, Henson et al. 2006). Marathon runners also exhibit elevated IL-10 levels for up to 1.5 h after the race, regardless of age or gender (Nieman, Henson et al. 2001). Cadet et al subjected patients suffering from Parkinson's Disease to a month of cyclic exercises and observed an increase in plasma IL-10 (Cadet, Zhu et al. 2003). While these studies give a fairly consistent view of increased peripheral IL-10 levels after exercise, little is known about CNS levels. Further research is necessary to evaluate the effects of exercise on central IL-10 concentrations and the interplay between IL-10 and the pro-inflammatory cytokines involved in the inflammatory cascade.

BDNF

Brain-derived neurotrophic factor (BDNF) is one of the most versatile and important neurotrophic factors in the brain (Radak, Kumagai et al. 2007). Abundant evidence exists that BDNF is essential for hippocampal function, synaptic plasticity, learning and neurogenesis

(Cotman, Berchtold et al. 2007; van Praag 2008; Mattson, Maudsley et al. 2004). Mice deficient in BDNF have severely impaired long term potentiation and deficits in hippocampal-dependent learning, whereas restoring BDNF to these mice reverses the findings (Berchtold, Chinn et al. 2005). BDNF interacts with the inflammatory cascade in that BDNF signaling is impaired by pro-inflammatory cytokines, and BDNF infused directly into brain tissue after ischemia decreases infarct size (Ding, Vaynman et al. 2006; Cotman, Berchtold et al. 2007). BDNF also increases the activity of free radical scavengers and can therefore protect neurons against free radical damage (Ang and Gomez-Pinilla 2007).

Exercise increases BDNF mRNA and protein concentrations in the brain (Mattson, Maudsley et al. 2004; Neper, Gomez-Pinilla et al. 2006; Berchtold, Chinn et al. 2005; Cotman and Berchtold 2002; Hicks, Boggs et al. 1998; Griesbach, Hovda et al. 2008; Adlard and Cotman 2004; Cechetti, Fochesatto et al. 2008; Radak, Toldy et al. 2006; Will, Galani et al. 2004). Rats with voluntary access to running wheels for 2-7 days showed significantly elevated BDNF mRNA in the hippocampus, cerebellum and frontal neocortex versus non-exercised controls, with a positive correlation between BDNF elevation and distance run (Neper, Gomez-Pinilla et al. 2006). Rats allowed either daily or alternating daily access to running wheels exhibited hippocampal BDNF levels that continued to rise even after 90 days of activity and remained elevated for up to 1 week after ceasing exercise (Berchtold, Chinn et al. 2005). When re-introduced to running wheels after a period of inactivity, a normally sub-threshold exercise routine caused a rapid return of BDNF protein to peak levels previously noted, suggesting that exercise creates a molecular memory for BDNF induction (Berchtold, Chinn et al. 2005). Eight weeks of swimming caused an elevation of BDNF in rats that returned to control levels after 6 weeks of detraining (Radak, Toldy et al. 2006). Thus, BDNF elevations appear to depend on continued exercise protocols.

The effects of exercise-induced BDNF elevations have also been studied following brain injury. After fluid percussion injury in rats, treadmill running increased hippocampal BDNF protein versus non-exercised controls bilaterally (Hicks, Boggs et al. 1998). After a controlled cortical impact, rats with access to a voluntary running wheel post-injury exhibited increased BDNF in the ipsilateral hippocampus versus sedentary controls (contralateral hippocampus not studied) (Griesbach, Hovda et al. 2008). Elevations in BDNF in the hippocampus ipsilateral to ischemic injury were equivalent in both exercised and sedentary rats, but a significant increase in BDNF levels in the contralateral hippocampus of only exercised rats was observed (Ploughman, Granter-Button et al. 2005). The equivalent concentrations observed ipsilateral to the ischemic area may be the result of BDNF already being maximally elevated in the injured area, precluding further exercise-induced elevation (Ploughman, Granter-Button et al. 2005). Since BDNF is thought to modulate neuronal survival and plasticity, this exercise-induced increase may lead to improved healing and functional recovery after injury.

Aging, neurodegenerative diseases and chronic uncontrollable stress decrease BDNF protein (Mattson, Maudsley et al. 2004). Previous studies have shown acute and repeated immobilization stress decrease hippocampal BDNF mRNA, likely due to the increase in cortisol seen with stress and its subsequent damaging effects in the hippocampus (Adlard and Cotman 2004; Smith, Makino et al. 1995; Ueyama, Kawal et al. 1997; Nibuya, Takahashi et al. 1999). However, one week of voluntary wheel running before forced swimming prevented the down-

regulation of hippocampal BDNF mRNA and improved behavioral measures of stress (Russo-Neustadt, Beard et al. 1999). Adlard et al showed that exercise alone increased hippocampal BDNF and stress alone decreased BDNF, but rats stressed after 3 weeks of voluntary running had BDNF mRNA concentrations significantly higher than control sedentary and stressed sedentary rats despite an elevated corticosterone level (Adlard and Cotman 2004). Thus, exercise may protect against stress-induced decreases in BDNF.

Human studies on BDNF are lacking due to the invasive procedures necessary to study the protein. However, since increased levels of BDNF correspond to increased learning and hippocampal function, exercise-induced increases in BDNF may benefit patients suffering from neurodegenerative diseases.

IGF-1

Insulin-like growth factor 1 (IGF-1) is a neurotrophic factor essential for nerve growth, neurotransmitter synthesis and neurotransmitter release (Radak, Kumagai et al. 2007). IGF1 is mainly produced in the liver, but is also synthesized in the brain (Ploughman, Granter-Button et al. 2005). IGF1 is believed to be functionally associated with BDNF and mediates glucose metabolism, tissue maintenance and insulin sensitivity (Cotman, Berchtold et al. 2007).

Exercise increases peripheral IGF-1 expression, and brain uptake of blood-borne IGF1 via the blood brain barrier (BBB) is essential for exercise-induced hippocampal neurogenesis (Carro, Trejo et al. 2001; Glasper, Llorens-Martin et al. 2009). Peripheral IGF-1 increases within 1 h after exercise, and IGF-1 gene expression in hippocampal neurons has been shown to increase several days after exercise onset (Cotman, Berchtold et al. 2007; Dalsgaard, Ott et al. 2004). Adult rats exercised on a voluntary wheel for 5 days showed significantly increased hippocampal IGF-1 mRNA compared to sedentary controls (Ding, Vaynman et al. 2006). Blocking IGF-1 via a peripheral anti-IGF-1 antibody prevented the running-induced increase in spine density on basal dendrites of CA1 pyramidal cells typically seen after 2 weeks of treadmill running in mice (Gasper, Llorens-Martin et al. 2009). Intra-hippocampal injection of anti-IGF1 prevents enhancement of spatial recall, suggesting hippocampal impairment (Cotman, Berchtold et al. 2007). Mice unable to produce IGF-1 from the liver with resultant low serum IGF-1 had reduced hippocampal neurogenesis and spatial learning deficits not improved by treadmill running, but administration of exogenous IGF-1 partially recovered the cognitive deficit and restored hippocampal neurogenesis (Trejo, Llorens-Martin et al. 2008). These results suggest that IGF1 production from tissues other than the liver is not sufficient to induce hippocampal neurogenesis after exercise and that IGF-1 is essential for exercise-induced hippocampal neurogenesis (Trejo, Llorens-Martin et al. 2008).

Exercise has been shown to ameliorate age- and injury- elated neuronal loss, and it is speculated that IGF-1 contributes to this phenomenon (Carro, Trejo et al. 2001). Carro et al subjected mice to partial lesions modeling neurodegeneration in the hippocampus, inferior olive, or cerebellum (Carro, Trejo et al. 2001). Mice exposed to voluntary running for 15d before partial hippocampal injury had unimpaired acquisition and retention scores in the water maze whereas sedentary mice were significantly impaired. Rats with inferior olive injuries regained full motor coordination in the exercised group but sedentary mice remained ataxic. Mice with cerebellar injuries and impaired motor coordination on the rotarod attained normal motor

performance after exercise training. Anti-IGF1 administration abrogated all exercise-induced improvements and resulted in neuronal damage indistinguishable from sedentary controls in all groups, while exogenous administration of IGF1 produced similar effects as exercise (Carro, Trejo et al. 2001). Fernandez et al observed similar results when mice rendered ataxic by deafferentation of the cerebellar cortex regained full motor function after IGF-1 administration (either intraventricular or subcutaneous) (Fernandez, Gonzalez et al. 1998). Thus, IGF-1 appears to be an essential mediator in exercise-induced recovery from neurodegeneration.

IGF-1 may exert its positive effects on brain health through a variety of ways. Possible mechanisms of neuroprotection may include modulation of apoptosis- and neuritogenesis-related proteins, modulation of calcium homeostasis via calbindin induction, and enhanced neuronal glucose metabolism since increased glucose consumption is a typical response to brain injury (Carro, Trejo et al. 2001). IGF-1 up-regulates glucose transporters and modulates glycolytic enzymes, further supporting its role in cerebral glucose metabolism (Carro, Trejo et al. 2001). Evidence suggests that IGF-1 mediates the effect of BDNF, since blocking IGF1 in vivo prevents induction of hippocampal BDNF in response to exercise and attenuates the exercise-dependent induction of synaptic proteins (Ding, Vaynman et al. 2006; Cotman, Berchtold et al. 2007). IGF1 increases neuronal levels of TrkB, the BDNF receptor, in hippocampal cultures thus increasing BDNF signaling (Cotman, Berchtold et al. 2007; McClusker, McCrea et al. 2006). Furthermore, peripheral IGF-1 infusion has been shown to qualitatively increase hippocampal BDNF staining (Ding, Vaynman et al. 2006; Carro, Trejo et al. 2001; McClusker, McCrea et al. 2006). Though exogenous administration of IGF-1 in rodent models led to improved cognition and reduced neurodegeneration, translation to clinical medicine has been difficult because of studies linking increased serum IGF-1 to cancer risk (Carro, Trejo et al. 2001). Thus, further research is required to determine exactly how IGF-1 mediates its neuroprotective effects to see if an effective and safe therapeutic target can be developed for humans.

Angiogenic Growth Factors

Vascular endothelial growth factor (VEGF) and angiopoietin (1 and 2) are members of a family of angiogenic growth factors whose combined action is necessary to initiate the formation, maturation and stabilization of new blood vessels (Ding, Luan et al. 2004). Angiogenesis typically occurs early in development and is decreased in the adult brain under normal conditions (Ding, Luan et al. 2004). It is generally accepted that the decrease in angiogenesis observed with aging is associated with decreased VEGF (Ding, Li et al. 2006).

Exercise increases angiogenesis in rodent models, and VEGF appears to be required for hippocampal neurogenesis observed with exercise (Ding, Li et al. 2006; Fabel, Fabel et al. 2003; Cotman and Berchtold 2002). Aged rats (22 months) subjected to treadmill running for 3 weeks exhibited elevated VEGF mRNA, VEGF protein, angiopoietin 1 mRNA and angiopoietin 2 mRNA in the frontoparietal cortex and dorsolateral striatum (Ding, Li et al. 2006), demonstrating that exercise can reverse the age-related decline in angiogenic factor induction. Young rats (3 months) also had increased VEGF and angiopoietin 1 and 2 mRNA in the frontoparietal cortex and dorsolateral striatum after 3 weeks of treadmill running (Ding, Luan et al. 2004). This mRNA overexpression decreased after 3 weeks without exercise but the vascular density remained elevated (Ding, Luan et al. 2004). Thus, exercise induced structural changes that persisted despite exercise cessation.

Similar to results found for IGF-1, blocking peripheral VEGF induction attenuates the proliferation of hippocampal cells typically seen with exercise in rodents (Fabel, Fabel et al. 2003; Cotman, Berchtold et al. 2007). While blocking peripheral VEGF resulted in equivalent hippocampal neurogenesis between exercised and sedentary mice, it did not suppress neurogenesis below baseline, suggesting that peripheral VEGF may not be involved in the central constitutive regulation of hippocampal neurogenesis (Fabel, Fabel et al. 2003).

The increase in angiogenic factors with exercise may be the result of hypoxia or glucose starvation (Ding, Li et al. 2006; Radak, Kumagai et al. 2007). Angiogenesis results in increased blood flow and nutrient supply to stressed tissues. The effects of VEGF on hippocampal neurogenesis may be directly related to VEGF-mediated signaling cascades and mitotic stimulation, or may be the effect of increased vascularization increasing nutrient and growth factor supply to the hippocampus (Fabel, Fabel et al. 2003). Peripheral production of both IGF-1 and VEGF increase with exercise and appear to be required for hippocampal neurogenesis. Whether these two growth factors respond to similar signals such as oxygen deprivation and hypoglycemia is unclear.

ROS

Reactive oxygen species (ROS) are continuously generated during aerobic metabolism. While they are vital to normal cell processes such as proliferation, growth, signaling and apoptosis, they can also damage lipids, DNA and proteins if not properly regulated (Radak, Kumagai et al. 2007; Radak, Sasvari et al. 2001). Reactive oxygen species are by-products of oxygen metabolism and include hydrogen peroxide, superoxide and hydroxyl radicals (Liu, Yeo et al. 2000). Measuring reactive oxygen molecules can be difficult due to short half-lives, but their effects can be measured indirectly by determining lipid oxidation, DNA damage, and carbonylation of proteins (Mooren and Volker 2001). Physiologic levels of ROS depend on cell type, age, and possibly the history of oxidative stress exposure but, in general, ROS levels increase with aging, injury and stress (Radak, Sasvari et al. 2001; Lima, Oliveira et al. 2009). The CNS is especially sensitive to ROS because the CNS contains high levels of iron, which interacts with hydrogen peroxide to generate highly reactive hydroxyl radicals (Radak, Kumagai et al. 2007; Forster, Dubey et al. 1996). It appears that accumulation of oxidative damage is associated with impaired brain function (Radak, Toldy et al. 2006).

It is generally believed that acute exercise induces free radical formation but regular exercise causes adaptation of the cellular antioxidant system and results in decreased oxidative damage (Cechetti, Fochesatto et al. 2008). Acute voluntary exercise in rats increases lipid peroxidation in the brain (Cechetti, Fochesatto et al. 2008). One hour of swimming increased lipid peroxidation and glutathione peroxidase activity in rat brains (Radak, Kumagai et al. 2007). However, eight weeks of swimming led to decreased brain free radicals that correlated with improved performance in a passive avoidance test in rats (Radak, Toldy et al. 2006). Free radical concentration reduction in the cerebellum persisted, but levels from other areas and performance in the passive avoidance test returned to non-exercised baseline values eight weeks after training stopped (Radak, Toldy et al. 2006). Nine weeks of swimming in both old and young rats led to significant decreases in brain protein carbonyl levels, indicating that exercise can reverse free radical accumulation associated with aging (Radak, Kaneko et al. 2001). Lifelong exercise (94 weeks) on a running wheel reduced DNA and lipid oxidation in rats, and

even 3 months of exercise initiated at 18 months of age reduced lipid oxidation indicating that exercise initiation late in life is still beneficial (Cui, Hofer et al. 2009). Somani et al found increased levels of antioxidant enzymes glutathione peroxidase, superoxide dismutase and catalase in the brains of exercised rats (Somani , Ravi et al. 1995; Somani and Husain 1996). Since exercise continually generates free radicals due to increased oxygen consumption, it may be that exercise exerts its beneficial effects by up-regulating antioxidants.

Exercise also appears to reduce oxidative damage after brain injury and immobilization stress. Voluntary exercise on a running wheel significantly decreased hippocampal carbonyl groups in rats after cortical controlled impact compared to sedentary controls (Griesbach, Hovda et al. 2008). Physical training before a fluid percussion injury (FPI) in rats protected against FPI-induced protein carbonylation and DNA damage as evidenced by decreased thiobarbituric acid-reactive substances (TBARS) in the cortex (Lima, Oliveira et al. 2009). Like TBI, immobilization stress also increases oxidative damage in the hippocampus and impairs performance in passive avoidance and open field tests in rats (Radak, Sasvari et al. 2001). However, swimming after immobilization decreased the oxidative damage of lipids, proteins and nuclear DNA compared to non-exercised immobilized controls and improved performance on behavioral tests (Radak, Sasvari et al. 2001).

While the above studies support the hypothesis that regular exercise decreases oxidative damage in the brain, some studies have shown no effect. Cechetti et al studied rats after 2 weeks of treadmill running and found no change in free radical levels, TBARS, or lipid oxidation in the hippocampus (Cechetti, Fochesatto et al. 2008). Ogonovsky studied rats subjected to moderate-, strenuous- and over-training swimming routines for 8 weeks and observed no change total brain oxidative damage of lipids and DNA (Ogonovsky, Berkes et al. 2005). However, there was a significant decrease in reactive carbonyl derivatives indicating decreased protein damage in the strenuous- and over-trained groups and an increase of proteasome complex in over-trained rats (Ogonovsky, Berkes et al. 2005). Liu et al studied oxidative damage in rat brain and central mitochondria after both 8 weeks of treadmill running and one episode of treadmill running to exhaustion (Liu, Yeo et al. 2000). Lipid peroxidation and carbonyl levels in the brain positively correlated with acute exercise, but there was no significant increase. Chronic exercise did not decrease carbonyl levels or DNA damage as seen with previous studies, but chronic exercise did significantly decrease lipid peroxidation. Chronic exercise also increased ascorbic acid and cysteine in the mitochondria, which act in anti-oxidant capacities and may contribute to the decreased lipid peroxidation observed (Liu, Yeo et al. 2000). Somani et al studied the effects of exercise on anti-oxidant properties of various brain portions, and found that regional variations observed in sedentary controls were enhanced with exercise (Somani, Ravi et al. 1995). Particularly, brain stem and corpus striatum appear to significantly up-regulate anti-oxidant enzymes in response to exercise whereas cortex and hippocampus are less affected (Somani, Ravi et al. 1995). Thus, the studies in which no changes were observed may be due to studying entire brain homogenates rather than specific portions. Additionally, these studies indicate that a certain intensity of exercise may be required to achieve oxidative protection and that brain mitochondria, with their active oxygen consumption and unique enzymatic environment, may respond differently to exercise-induced neuroprotection than the rest of the brain.

CONCLUSION

Exercise promotes a healthy lifestyle and may contribute to improved neuronal viability via its modulation of the inflammatory cascade. Generally, regular exercise appears to decrease circulating pro-inflammatory cytokines such as IL-1 β and IL-6 while increasing anti-inflammatory IL-10. While exercise increases pro-inflammatory TNF- α , the gradual increase observed with regular exercise seems to provide protection against ischemic insults. Additionally, exercise increases growth factors BDNF, IGF-1 and VEGF while decreasing oxidative damage from ROS. These combined effects of exercise have been shown to decrease infarct size after ischemia, decrease performance degradation after TBI and protect against neurodegenerative processes.

Several questions remain to be answered regarding the specific effects and interaction of the mediators of the inflammatory cascade. For example, it is still unclear what intensity and type of exercise leads to the optimum concentrations of growth factors, cytokines and ROS and whether too much exercise is harmful. Environmental enrichment has recently been shown to have positive effects on neurological processes and inflammatory mediators, and it may be that the combination of exercise and cognitive enrichment is synergistic and better than exercise alone. Additionally, there are a variety of other cytokines and growth factors (NGF, FGF, etc) that are less well studied and perhaps unknown that may be crucial in mediating the positive effects of exercise. Few studies examined the duration of change in inflammatory mediator levels after exercise cessation but it remains unclear whether permanent changes can be observed despite exercise cessation and, if so, how much exercise is required. Prophylactic exercise is difficult to initiate in human populations because it is unknown if and when a brain injury will occur, but evidence of lasting effects after finite exercise regimes may benefit at-risk populations (Lima, Oliveira et al. 2009). Overall, abundant evidence exists that exercise promotes both general and brain health, and it is crucial to elucidate specific pathways and interactions so that possible pharmacologic targets for neurologic conditions may be developed.

REFERENCES

Adlard PA and Cotman CW. Voluntary exercise protects against stress-induced decreases in brain-derived neurotrophic factor protein expression. *Neuroscience* 124 (2004) 985-992.

Ang ET and Gomez-Pinilla F. Potential therapeutic effects of exercise to the brain. *Curr Med Chem* 14 (2007) 2564-2571.

Banks WA, Kastin AJ and Gutierrez EG. Penetration of interleukin-6 across the murine blood-brain barrier. *Neurosci Lett* 179:1-2 (1994) 53-56.

Barone FC, Arvin B, White RF, Miller A, Webb CL, Willette RN, Lysko PG and Feuerstein GZ. Tumor necrosis factor- α : A mediator of focal ischemic brain injury. *Stroke* 28 (1997) 1233-1244.

Berchtold NC, Chinn G, Chou M, Kesslak JP and Cotman CW. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. *Neuroscience* 133 (2005) 853-861.

Cadet P, Zhu W, Mantione K, Rymer M, Dardik I, Reisman S, Hagberg S and Stefano GB. Cyclic exercise induces anti-inflammatory signal molecule increases in the plasma of Parkinson's patients. *Internat J Mol Med* 12 (2003) 485-92.

Carro E, Trejo JL, Busiguina S and Torres-Aleman I. Circulating insulin-like growth factor 1 mediates the protective effects of physical exercise against brain insults of different etiology and anatomy. *J Neuroscience* 21:15 (2001) 5678-5684.

Castaneda C, Gordon PL, Parker RC, Uhlin KL, Roubenoff R and Levey AS. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. *Am J Kidney Dis* 43:4 (2004) 607-616.

Cechetti F, Fochesatto C, Scopel D, Nardin P, Goncalves CA, Netto CA and Siqueira IR. Effect of a neuroprotective exercise protocol on oxidative state and BDNF levels in the rat hippocampus. *Bran Research* 1188(2008) 182-188.

Chennaoui M, Drogou C and Gomez-Merino D. Effects of physical training on IL-1beta, IL-6 and IL-1ra concentrations in various brain areas of the rat. *Eur Cytokine Netw* 26:19 (2008) 17-23.

Colbert LH, Davis JM, Essig DA, Ghaffar A and Mayer EP. Tissue expression and plasma concentrations of TNFalpha, IL-1beta and IL-6 following treadmill exercise in mice. *Int J Sports Med* 22:4 (2001) 261-267.

Cotman Cw and Berchtold NC. Exercise: A behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25:6 (2002) 295-301.

Cotman CW, Berchtold NC and Christie L. Exercise builds brain health: Key roles of growth factor cascades and inflammation. *Trends Neurosci* 30:9 (2007) 464-472.

Cui L, Hofer T, Rani A, Leeuwenburgh C and Foster TC. Comparison of lifelong and late life exercise on oxidative stress in the cerebellum. *Neurobiol Aging* 30:6 (2009) 903-909.

Dalsgaard MK, Ott P, Dela F, Juul A, Pedersen BK, Warberg J, Fahrenkrug J and Secher NH. The CSF and arterial to internal jugular venous hormonal differences during exercise in humans. *Exp Physiol* 89:3 (2004) 271-277.

Ding YH, Young CN, Luan X, Li J, Rafols JA, Clark JC, McAllister JP and Ding Y. Exercise preconditioning ameliorates inflammatory injury in ischemic rats during reperfusion. *Acta Neuropathol* 109 (2005) 237-246.

Ding YH, Mrizek M, Lai Q, Wu Y, Reyes R, Li J, Davis WW and Ding Y. Exercise preconditioning reduces brain damage and inhibits TNF- α receptor expression after hypoxia/reoxygenation: An *in vivo* and *in vitro* study. *Curr Neurovasc Res* 2 (2006) 263-271.

Ding YH, Li J, Yao WX, Rafols JA, Clark JC and Ding Y. Exercise preconditioning upregulates cerebral integrins and enhances cerebrovascular integrity in ischemic rats. *Acta Neuropathol* 112 (2006) 74-84.

Ding Q, Vaynman S, Akhavan M, Ying Z and Gomez-Pinilla F. Insulin-like growth factor 1 interfaces with brain-derived neurotrophic factor-mediated synaptic plasticity to modulate aspects of exercise-induced cognitive function. *Neuroscience* 140 (2006) 823-822.

Ding YH, Luan XD, Rafols JA, Guthinkonda M, Diaz FG and Ding Y. Exercise-induced overexpression of angiogenic factors and reduction of ischemia/reperfusion injury in stroke. *Curr Neurovasc Res* 1 (2004) 411-420.

Ding YH, Li J, Zhou Y, Rafols JA, Clark JC and Ding Y. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. *Curr Neurovasc Res* 3 (2006) 15-23.

Donovan DC, Jackson CA, Colahan PT, Norton N and Hurley DJ. Exercise-induced alterations in pro-inflammatory cytokines and prostaglandin F2alpha in horses. *Vet Immunol Immunopathol* 118:3-4 (2007) 263-269.

Fabel K, Fabel K, Tam B, Kaufer D, Baiker A, Simmons N, Kuo CJ and Palmer TD. VEGF is necessary for exercise-induced adult hippocampal neurogenesis. *Eur J Neurosci* 18 (2003) 2803-2812.

Fassbender K, Rossol S, Kammer T, Daffertshofer M, Wirth S, Dollman M and Hennerici M. Proinflammatory cytokines in serum of patients with acute cerebral ischemia: kinetics of secretion and relation to the extent of brain damage and outcome of disease. *J Neurol Sci* 122:2 (1994) 135-139.

Febbraio MA and Pedersen BK. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB* 16 (2002) 1335-1347.

Fernandez AM, Gonzalez de la Vega A and Torres-Aleman I. Insulin-like growth factor 1 restores motor coordination in a rat model of cerebella ataxia. *Proc Natl Acad Sci* 95 (1998) 1253-1258.

Forster MJ, Dubey A, Dawson KM, Stutts WA, Lal H and Sohal RS. Age-related losses of cognitive function and motor skills in mice are associated with oxidative protein damage in the brain. *Proc Natl Acad Sci* 93 (1996) 4765-4769.

Glasper ER, Llorens-Martin MV, Leuner B, Gould E and Trejo JL. Blockade of insulin-like growth factor 1 has complex effects on structural plasticity in the hippocampus. *Hippocampus* 14 (2009).

Goldhammer E, Tanchilevitch A, Maor I, Beniamini Y, Rosenschein U and Sagiv M. Exercise training modulates cytokines activity in coronary heart disease patients. *Int J Cardiol* 100:1 (2005) 93-99.

Goodman JC, Robertson CS, Grossman RG and Narayan RK. Elevation of tumor necrosis factor in head injury. *J Neuroimmunol* 30:2-3 (1990) 213-217.

Griesbach GS, Hovda DA, Gomez-Pinilla F and Sutton RL. Voluntary exercise or amphetamine treatment, but not the combination, increases hippocampal brain-derived neurotrophic factor and synapsin 1 following cortical contusion injury in rats. *Neuroscience* 154:2 (2008) 530-540.

Guo M, Lin V, Davis W, Huang T, Carranza A, Sprague S, Reyes R, Jimenez D and Ding Y. Preischemic induction of TNF-alpha by physical exercise reduces blood-brain barrier dysfunction in stroke. *J Cereb Blood Flow Metab* 28:8 (2008) 1422-1430.

Hicks RR, Boggs A, Leider D, Kraemer P, Brown R, Scheff SW and Seroogy KB. Effects of exercise following lateral fluid percussion brain injury in rats. *Rest Neurol and Neurosci* 12 (1998) 41-16.

Krakauer T. IL-10 inhibits the adhesion of leukocytic cells to IL-1-activated human endothelial cells. *Immunol Letters* 45 (1995) 61-65.

Lima FD, Oliveira MS, Furian AF, Souza MA, Rambo LM, Riberio LR, Silva LRA, Retamoso LT, Hoffman MS, Magni DV, Pereira L, Fighera MR, Mello CF and Royes LFF. Adaptation to oxidative challenge induced by chronic physical exercise prevents Na^+/K^+ -ATPase activity inhibition after traumatic brain injury. *Brain Research* 1279 (2009) 147-155.

Liu J, Yeo HC, Overvik-Douki E, Hagen T, Doniger SJ, Chu DW, Brooks GA and Ames BN. Chronically and acutely exercised rats: biomarkers of oxidative stress and endogenous antioxidants. *J Appl Physiol* 89 (2000) 21-28.

Mattson MP, Maudsley S and Martin B. A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. *Ageing Res Rev* 3 (2004) 445-464.

McCusker RH, McCrea K, Zunich S, Dantzer R, Broussard SR, Johnson RW and Kelley KW. Insulin-like growth factor-1 enhances the biological activity of brain-derived neurotrophic factor on cerebrocortical neurons. *J Neuroimmunol* 179 (2006) 186-190.

Mooren FC and Volker K. Exercise-induced modulation of intracellular signaling pathways. *Exer Immunol Rev* 7 (2001) 32-65.

Morganti-Kossmann MC, Rancan M, Stahel PF and Kossmann T. Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr Opin Crit Care* 8:2 (2002) 101-105.

Moyna NM, Acker GR, Fulton JR, Weber K, Goss FL, Robertson RJ, Tollerud DJ and Rabin BS. Lymphocyte function and cytokine production during incremental exercise in active and sedentary males and females. *Int J Sports Med* 18:8 (1996) 585-591.

Mussi RK, Camargo EA, Ferreira T, DeMoraes C, Delbin MA, Toro IF, Brancher S, Landucci EC, Zanesco A and Antunes E. Exercise training reduces pulmonary ischaemia-reperfusion-induced inflammatory responses. *Eur Respir J* 31:3 (2008) 645-649.

Natelson BH, Zhou X, Ottenweller JE, Bergen MT, Sisto SA, Drastal S, Tapp WN and Gause WL. Effect of acute exhausting exercise on cytokine gene expression in men. *Int J Sports Med* 17:4 (1996) 299-302.

Nepper SA, Gomez Pinilla F, Choi J and Cotman C. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res* 726 (1996) 49-56.

Nibuya M, Takahashi M, Russell D, Duman R. Repeated stress increase catalytic TrkB mRNA in rat hippocampus. *Neurosci Lett* 267 (1999) 81-84.

Nichol KE, Poon WW, Parachikova AI, Cribbs DH, Glabe CG and Cotman CW. Exercise alters the immune profile in Tg2576 Alzheimer mice toward a response coincident with improved cognitive performance and decreased amyloid. *J Neuroinflam* 5:13 (2008) 9.

Nickerson M, Elphick GF, Campisi J, Greenwood BN and Fleshner M. Physical activity alters the brain Hsp72 and IL-1 β responses to peripheral *E. coli* challenge. *Am J Physiol Regul Integr Comp Physiol* 289 (2005) R1665-R1674.

Nielsen AR and Pedersen BK. The biological roles of exercise-induced cytokines: IL-6, IL-8 and IL-15. *Appl Physiol Nutr Metab* 32 (2007) 833-839.

Nieman DC, Henson DA, Smith LL, Utter AC, Vinci DM, Davis JM, Kaminsky DE and Shute M. Cytokine changes after a marathon race. *J Appl Physiol* 91:1 (2001) 109-114.

Nieman DC, Henson DA, Davis JM, Dumke CL, Utter AC, Murphy EA, Pearce S, Gojanovich G, McAnulty SR and McAnulty LS. Blood leukocyte mRNA expression for IL-10, IL-1Ra, and IL-8, but not IL-6 increases after exercise. *J Interferon Cytokine Res* 26:9 (2006) 668-674.

Nybo L, Nielsen B, Pedersen BK, Moller K and Secher NH. Interleukin-6 release from the human brain during prolonged exercise. *J Physiol* 1:542 (Pt3) (2002) 991-995.

Ogonovszky H, Berkes I, Kumagai S, Kaneko T, Tahara S, Goto S and Radak Z. The effects of moderate-, strenuous- and over-training on oxidative stress markers, DNA repair, and memory, in rat brain. *Neurochem Internat* 46:8 (2005) 635-640.

Oitzl MS, van Oers H, Schobitz B and de Kloet ER. Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. *Brain Res* 613:1 (1993) 160-163.

Ozenci V, Kouwenhoven M and Link H. Cytokines in multiple sclerosis: Methodological aspects and pathogenic implications. *Multiple Sclerosis* 8 (2002) 396-404.

Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K and Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. *Eur J Appl Physiol* 95 (2005) 514-521.

Petersen AMW and Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 98 (2005) 1154-62.

Ploughman M, Granter-Button S, Chernenko G, Tucker BA, Mearow KM and Corbett D. Endurance exercise regimens induce differential effects on brain-derived neurotrophic factor, synapsin-1 and insulin-like growth factor 1 after focal ischemia. *Neuroscience* 136 (2005) 991-1001.

Radak Z, Kaneko T, Tahara S, Nakamoto H, Pucsok J, Sasvari M, Nyakas C and Goto S. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. *Neurochem Internat* 38 (2001) 17-23.

Radak Z, Sasvari M, Nyakas C, Kaneko T, Tahara S, Ohno H and Goto S. Single bout of exercise eliminates the immobilization-induced oxidative stress in rat brain. *Neurochem Internat* 39 (2001) 33-38.

Radak Z, Toldy A, Szabo Z, Siamilis S, Nyakas C, Silye G, Jakus J and Goto S. The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochem Internat* 49 (2006) 387-392.

Radak Z, Kumagai S, Taylor AW, Naito H and Goto S. Effects of exercise on brain function: role of free radicals. *Appl Physiol Nutr Metab* 32 (2007) 942-946.

Robson-Ansley PJ, de Milander L, Collins M, Noakes TD. Acute interleukin-6 administration impairs athletic performance in healthy, trained male runners. *Can J Appl Physiol* 29 (2004) 411-418.

Romeo J, Jimenez-Pavon D, Cervantes-Borunda M, Warnberg J, Gomez-Martinez S, Castillo MJ and Marcos A. Immunological changes after a single bout of moderate-intensity exercise in a hot environment. *J Physiol Biochem* 64:3 (2008) 197-204.

Russo-Neustadt A, Beard RC and Cotman CW. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharm* 21 (1999) 679-682.

Secher NH, Seifert T and Van Lieshout JJ. Cerebral blood flow and metabolism during exercise: implications for fatigue. *J Appl Physiol* 104 (2008) 306-314.

Sharma V, Mishra M, Chosh S, Tewari R, Basu A, Seth P and Sen E. Modulation of interleukin-1beta mediated inflammatory response in human astrocytes by flavonoids: Implications in neuroprotection. *Brain Res Bull* 73 (2007) 55-63.

Smith LL, Anwar A, Fragen M, Rananto C, Johnson R and Holbert D. Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise. *Eur J Appl Physiol* 82: 1-2 (2000) 61-67.

Smith LL, McKune AJ, Semple SJ, Sibanda E, Steel H and Anderson R. Changes in serum cytokines after repeated bouts of downhill running. *Appl Physiol Nutr Metab* 32:2 (2007) 233-240.

Smith M, Makino S, Kvetnansky R and Post R. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci* 15 (1995) 1768-1777.

Somani SM, Ravi R and Rybak LP. Effect of exercise training on antioxidant system in brain regions of rat. *Pharmacol Biochem Beh* 50:4 (1995) 635-639.

Somani SM and Husain K. Exercise training alters kinetics of antioxidant enzymes in rat tissues. *Biochem Mol Biol Int* 38:3 (1996) 587-595.

Steensberg A, Dalsgaard MK, Secher NH and Pedersen BK. Cerebrospinal fluid IL-6, HSP72, and TNF-alpha in exercising humans. *Brain Behav Immun* 20:6 (2006) 585-589.

Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, Dantzer R and Kelley KW. Interleukin-10 in the brain. *Crit Rev Immunol* 21:5 (2001) 427-449.

Trejo JL, Llorens-Martin MV and Torres-Aleman I. The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-1-dependent mechanism related to hippocampal neurogenesis. *Mol Cell Neurosci* 37 (2008) 402-411.

Tsakiri N, Kimber I, Rothwell NJ and Pinteaux E. Differential effects of interleukin-1 alpha and beta on interleukin-6 and chemokine synthesis in neurons. *Mol Cell Neurosci* 38 (2008) 259-265.

Ueyama T, Kawal Y, Nemoto K, Sekimoto M, Tone S and Tenba E. Immobilization stress reduced the expression of neurotrophins and their receptors in the rat brain. *Neurosci Res* 28 (1997) 103-110.

Van Praag H. Neurogenesis and exercise: past and future directions. *Neuromol Med* 10 (2008) 128-140.

Van Wagoner, NJ and Benveniste EN. Interleukin-6 expression and regulation in astrocytes. *J Neuroimmunol* 100 (1999) 124-139.

Vitkovic L, Maeda S and Sternberg E. Anti-inflammatory cytokines: expression and action in the brain. *Neuroimmunomodulation* 9:6 (2001) 295-312.

Wallenius V, Wallenius K, Ahren B, Rudling M, Carlsten H, Dickson SL, Ohlsson C and Jansson JO. Interleukin-6-deficient mice develop mature-onset obesity. *Nat Med* 8:1 (2002) 75-79.

Wang CX, Olschowka JA and Wrathall JR. Increase of interleukin-1 β mRNA and protein in the spinal cord following experimental traumatic injury in the rat. *Brain Research* 759 (1997) 190-196.

Wang CX, Shuaib A. Involvement of inflammatory cytokines in central nervous system injury. *Prog Neurobiol* 67 (2002) 161-172.

White LJ and Castellano V. Exercise and brain health – implications for multiple sclerosis: Part II – Immune factors and stress hormones. *Sports Med* 38:3 (2008) 179-186.

Whitney NP, Eidem TM, Peng H, Huang Y and Zheng JC. Inflammation mediates varying effects in neurogenesis: relevance to the pathogenesis of brain injury and neurodegenerative disorders. *J Neurochem* 108 (2009) 1343-1359.

Will B, Galani R, Kelche C and Rosenzweig MR. Recovery from brain injury in animals: relative efficacy of environmental enrichment, physical exercise or formal training (1990-2002). *Prog Neurobiol* 72 (2004) 167-182.